REMARKS

The Official Action dated November 18, 2002 and the Advisory Action dated February 10, 2003 have been carefully considered. The changes presented herewith, taken with the following remarks, are believed sufficient to place this application in condition for allowance. Reconsideration is respectfully requested.

By the present amendment, claims 1, 30, 33 and 34 are amended to recite the embodiment wherein the second intelligent polymer component comprises a mixture of hydroxyethylcellulose (HEC) and hydroxypropyl methyl cellulose (HPMC). Claim 14 is amended to correct a typographical error and claim 25 is amended to depend from claim 1. A Version with Markings Showing Changes Made is attached. It is believed that these changes do no involve any introduction of new matter and do not raise any new issues subsequent to final rejection, whereby entry of the amendments is believed to be in order and is respectfully requested.

Claims 1-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the Sangekar et al U.S. Patent 5,000,962 in view of the Stupak et al U.S. Patent 5,162,117. The Examiner stated that Sangekar discloses a formulation comprising a swellable polymer that may include HPMC, HPC, HMC, HEC and HPC which can be used alone or in combination, referencing column 2, lines 57-61. The Examiner also stated that Sangekar teaches the presence of a binder in the composition that may be ethylcellulose at column 3, lines 51-55, and inclusion of excipients and lubricants. The Examiner thus concluded that this reference teaches the combination of HPMC and HEC and further in combination with EC for the creation of a long acting pharmaceutical formulation.

This rejection is traversed and reconsideration is respectfully requested. The combination of the teachings of these two cited references does not suggest the presently claimed invention, or the improvements thereof.

As defined by present claims 1, 14, 19, 23, 30, 33 and 34, the invention is directed to controlled release pharmaceutical compositions and methods for their preparation, which employ, *inter alia*, at least one pharmaceutically active substance, a first intelligent polymer component, and a second intelligent polymer component comprising a mixture of hydroxyethylcellulose (HEC) and hydroxypropyl methyl cellulose (HPMC). According to claims 14, 19, 23, 30 and 34, the first intelligent polymer component comprises ethylcellulose (EC). Applicants previously provided detailed scientific showings in declaration form to establish that one cannot simply "mix and match" or "substitute" polymers since different dissolution profiles will result, whereby individual polymers are not interchangeable. The Examiner's attention is again directed to the showings in the Declaration which demonstrate the nonobviousness of the presently claimed compositions.

Sangekar is directed to a tablet composition comprising diltiazem and a swellable hydrophilic polymer. As taught specifically in column 2, lines 57-61, examples of the swellable hydrophillic polymers include: "hydroxypropylmethyl cellulose; hydroxypropylcellulose; methylcellulose; hydroxymethylcellulose; hydroxyethylcellulose; hydroxypropylcellulose, which can be used alone or in combination; carboxymethyl cellulose and the sodium salt thereof, which can be used alone or in combination; and other hydrocolloids, such as acacia and guar gum. The preferred swellable hydrophillic polymer is either hydroxypropylmethylcellulose or hydroxypropylcellulose."

Therefore, this passage does not teach combining any of the listed polymers. Instead, only the hydroxypropylcellulose (HPC) and the carboxymethyl cellulose (CMC) and the sodium salt thereof are taught for use with other polymers. Furthermore, Sangekar does not

teach what combination would be made. Thus, the only two polymers that are taught that could be combined are HPC and CMC, which are not claimed in any of independent claims 1, 14, 19, 23, 30, 33 or 34. This passage does not teach using a combination of polymer that would include HPMC and HEC as presently claimed, particularly with EC. Sangekar in fact teaches away from using a combination of polymers as presently claimed since the preferred swellable hydrophillic polymer is taught in column 2 to be either HPMC or HPC, and only HPC and CMC are taught as combinable. Moreover, while Sangekar further teaches the use of a binder that may comprise HPMC, HPC, CMC, EC and most preferred povidone, this teaching does not provide a suggestion for a combination with the polymers disclosed in column 2 to result in the compositions presently claimed. Finally, examples 1-5 of Sangekar do not disclose a combination of any polymer other than HPMC and EC, and Applicants find no teaching or suggestion of the combination of HEC and HPMC as presently claimed, particularly with EC. Thus, Sangekar does not teach or provide any guidance with respect to making any combination of polymers as presently claimed, and as such, cannot render the present claims obvious.

Stupak is relied upon for teaching of excipients. Stupak does not, however, suggest the combination of polymers as recited in the present independent claims. Therefore, the additional teachings of Stupak cannot in combination with Sangekar render obvious the invention as recited in the present claims.

For obviousness to be determined, the (1) claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) reasonable expectation of success is the standard with which obviousness is determined.

Neither Sangekar nor Stupak suggest the combination of polymers claimed. Further, neither reference suggests any desirability of making the claimed combination or provides any guidance as to how to make such combination. The Examiner's attention is again drawn to the previously filed declaration which disclosed that different polymers are not readily interchangeable.

In view of the above submitted arguments, it is evident that the combination of the teachings of the references does not suggest to one skilled in the art that such specific elements of each reference may be combined to provide the presently claimed invention. Furthermore, there is no teachings in any of the cited references which would lead one skilled in the art to expect that any such combination of selected teachings would lead to a successful extended release formulation as presently claimed. For these reasons, the presently rejected claims cannot be considered to be obvious in view of the combined teachings of the cited art, whereby the rejection under 35 U.S.C. § 103(a) has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejection under 35 U.S.C. § 103(a) and places the present application in condition for allowance.

Reconsideration and an early allowance are requested.

Respectfully submitted,

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VERSION WITH MARKINGS SHOWING CHANGES MADE

Claims 1, 14, 25, 30, 33 and 34 are amended as follows:

1. (Fifth Amendment) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising [hydroxyethylcellulose or] a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for up to at least 20 hours.

14. (Amended) A controlled release pharmaceutical composition comprising:

(a) from about 0.5% to about 70% by weight of a pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) not less than about 5% by weight ethylcellulose;

(c) about 1:100 to 100:1 [hydroxycellulose] <u>hydroxyethylcellulose</u> and hydroxypropyl methyl cellulose by weight;

(d) about 0.25% to 5% excipients; and

(e) about 0.5% to 15% surface active agents.

25. (Amended) The composition of claim 1, encased in [A process for preparing] a "stealth" encasement[, said] formed by a process comprising preparing a first solution of methacrylic acid copolymer type A and/or type B in ethanol, preparing a second solution of PEG 600 in water, adding talc, pigment and titanium dioxide to the first solution and then incorporating the second solution and mixing vigorously under high shear mixing conditions.

30. (Fourth Amendment) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component comprising ethylcellulose

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising [hydroxyethylcellulose, or hydroxypropyl methyl cellulose, or] a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for up to at least 20 hours; and

wherein components (a), (b) and (c) are formulated as a homogeneous matrix and said composition has a moisture content of less than 3%.

33. (Amended) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising [hydroxyethylcellulose or] a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition.

34. (Amended) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component comprising ethylcellulose

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising [hydroxyethylcellulose, or hydroxypropyl methyl cellulose, or] a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition; and

wherein components (a), (b) and (c) are formulated as a homogeneous matrix and said composition has a moisture content of less than 3%.

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